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Long-Term Follow-Up of Cervical Intraepithelial Neoplasia Treated With Minimal Conization by Carbon Dioxide Laser

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Background and Objective: **Minimal conization with carbon dioxide laser (CO_2) for safe diagnosis and treatment of cervical intraepithelial neoplasia (CIN) 1–3 has been utilized for 15 years. To evaluate the results of 15 years' follow-up.**
Study Design/Materials and Methods: **Clinical prospective study: 2,903 non-pregnant women whose cervicovaginal smear revealed CIN 1–3, confirmed by colposcopy, were referred for minimal conization treatment (LMC). This outpatient free-hand excision is performed under local anesthesia with a 60-W continuous laser beam focused to a 0.1-mm spot size, giving a power density of 165,000 W/cm^2. Adjuvant cervical curettage is done routinely.**
Results: **Complications after the procedure were insignificant. Histopathological investigation revealed invasive carcinoma in 1.2% of the minicones. The primary cure rate was 96.1%. In the life table analysis of the patients the cumulative risk of recurrence for all forms of CIN was 0.89% at year 5, 1.36% at year 10, and 3.02% at year 15. There was no sudden onset carcinoma during the follow-up period.**
Conclusion: **Minimal conization is a safe, effective treatment for CIN and early forms of microinvasive carcinoma. Invasive carcinoma can be detected early and should be treated without delay. The cumulative risk of developing new CIN is 3.02% at year 15 and there is no risk of sudden-onset invasive carcinoma following this procedure. Lasers Surg. Med. 20:461–466, 1997.**

Key words: cervical carcinoma; cervical neoplasia; conization; follow-up; laser

INTRODUCTION

During recent decades CO_2 laser ablation for treatment of CIN has become one of the most convenient treatment modalities worldwide [1–3]. This destructive method, which used to evaporate the cervix by means of a laser connected to the colposcope, does not afford the possibility of histopathologically examining the cervical tissue so destroyed. The minimal laser conization technique described by Bekassy et al. [4,5] implies free-hand excision of a 5-mm-thick, slightly conical tissue specimen. This resects the same cervical tissue volume as destroyed with laser ablation, but enables adequate histopathological examination of all the excised tissue including the entire transformation zone and 5 mm of the endocervical canal. Routine cervical curettage after removal of the cone specimen is included in the procedure. This prospective study considers the results obtained, including follow-up, after minimal laser conization.

MATERIALS AND METHODS

Over a period of 15 years, from July 1979 to June 1994, from about 7,000 women with abnor-

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mal cervical smears, mainly from the ongoing mass screening program in Malmöhus county in southern Sweden, 2,903 non-pregnant subjects underwent LMC with CO_2 laser. In all cases they were treated at the Department of Gynecology and Obstetrics, University Hospital Lund, Sweden, if 1) the latest cervical smear demonstrated CIN 1, 2, or 3, 2) if there was colposcopic evidence of at least ectocervical CIN, and 3) the extent of the ectocervical lesion was deemed to be beyond the scope of complete eradication by means of punch biopsy. The term CIN3 also denotes carcinoma in situ (CIS) findings. Only 3.9% (n = 113) of the patients with remaining CIN, all nulliparous young women of childbearing age with colposcopically normal appearance of the ectocervix and histological evidence of endocervical CIN 1–3, were included.

The LMC procedure was performed under local anesthesia on an outpatient basis, using a hand-directed CO_2 scalpel, to excise a 5-mm (range 3–8 mm) thick conical tissue disc from the cervix, containing the entire transformation zone. The procedure also included routine cervical curettage [4,5]. During the early part of the study period a Sharplan 733 surgical CO_2 laser was used, and was replaced from June 1988 with a Sharplan 1060 instrument (Laser Industries, Tel Aviv, Israel). Their spot size was focused to 0.2 mm and 0.1 mm, respectively, using a continuous laser beam of 40 W and 60 W output, respectively, and maintaining a power density of about 80,000 W/cm^2 and 165,000 W/cm^2, respectively.

Histopathologically, the minimal cones with CIN at the ectocervical, endocervical or lateral lines of resection—or if CIN was found in the curettage from cervical mucosa—were classified as denoting an involved, "positive margin." If the lines of resection were not involved, the cones were designated "free margins." "Uncertain margins" designated cones in which involvement of the resection lines was difficult to evaluate due to a lack of intact epithelium, to thermic damage, or to faulty orientation.

To prevent postoperative hemorrhage, peroral antifibrinolytic therapy with 1 g tranexamic acid (Cyklokapron^R, Pharmacia, Uppsala, Sweden) was prescribed three times daily and maintained for 2 weeks [6].

The first check-up was made 6 months after the LMC procedure. Subsequently, if the patient with free margins in the minimal cone had both normal colposcopy and cervical smear results, the next check-up was scheduled 1 year later by a specially trained midwife. If the cone had 'uncertain margins' two check-ups with a 6-month interval were made before the annual check-ups. After 5 years of observation at yearly intervals, the check-up period was extended to 1.5 to 2 year intervals.

"Residual disease" was regarded as persisting CIN after treatment when cytology, colposcopy, directed biopsy, or cervical curettage at the first or second visit showed evidence of residual disease requiring further treatment, whereas "recurrent disease" was CIN occurring after two check-ups with normal colposcopy and cervical smear findings. This means a disease-free period of 1 year at least and, in the great majority of cases, 1.5 years disease-free. Patients with invasive carcinoma in the minicones underwent immediate adjuvant appropriate surgery according to the carcinoma stage and cases of microinvasive carcinoma according to the desire of the patient for preserved fertility.

The risk of recurrent CIN was assessed by means of a standard life table method.

RESULTS

A total of 2,903 patients were treated for CIN 1–3 (Table 1). Their age distribution, with ultimate histopathological diagnosis of CIN or carcinoma taken into consideration, is shown in Table 2A and 2B. Five hundred eleven (17.6%) patients were monitored outside of our catchment area or were lost to follow-up. Of the remaining 2,392 patients, 21 (0.88%) died of unrelated causes (Table 3); however, they were followed up for between 2 and 5 years. About 30% (n = 715) of those patients free from gynecological complaints were seen by a midwife for check-up on at least one occasion during the follow-up period.

The relationship between the pretreatment CIN diagnosis based on a cervical smear and the ultimate histopathological finding from the minicone is presented in Table 1. The significance of margins involved is shown in Table 4 which also shows the number of second treatments performed because of persisting CIN.

Staging of invasive carcinoma was done according to the FIGO [7].

Of the 35 patients with invasive carcinoma (1.2%) reported in Table 1, 14 patients (eight stage IB carcinoma and six stage IA2) were treated with modified Wertheim & Meigs radical hysterectomy including a vaginal cuff resection and pelvic lymphadenectomy, but with preserva-

TABLE 1. Relationship Between Pretreatment Cytology and Histopathological Results From the Minicones in 2,903 Women

	Histopathology of minicone specimens								
						Invasive carcinoma			
Cytologic diagnosis	Benign	CIN1	CIN 2	CIN 3/CIS	CIS + adeno-CIS	1A1	1A2	1B	Total	%
CIN 3/CIS	2	51	145	808	74	10	7	6[a]	1,103	38.0
CIN 2	2	77	453	306	37	4	2[a]	2	883	30.4
CIN 1	6	378	273	116	8	2	1		784	27.0
Uncertain squamous atypia	3	4	8	18	11				44	1.5
Warty atypia	10	21	29	26	2	1			89	3.1
n	23	531	908	1,274	132	17	10	8	2,903	100.0
%	0.8	18.3	31.3	43.9	4.5	0.6	0.3	0.3	100.0	
				48.4%	1.2%		1.2%			

[a]One patient with coexistent adenocarcinoma.

TABLE 2A. Age Distribution of the 2,903 Patients Treated by Laser Minimal Conization

Age in years	n	%
⩽19	67	2.3
20–29	572	19.7
30–39	1,271	43.8
40–49	746	25.7
50–59	195	6.7
⩾60	52	1.8

TABLE 2B. Age Distribution of Miniconized Women With Regard to the Histopathological Finding

	n	Range (in years)	Mean
All patients	2,903	17–76	31.5
Carcinoma	35	26–42	33.1
CIN3/CIS	1,103	17–48	28.9
CIN2	883	19–67	27.7
CIN1	784	18–54	29.8
Uncertain atypia	44	23–76	47.8
Warty atypia	89	17–33	24.3

TABLE 3. Unrelated Deaths and Intercurrent Diseases in 2,392 Previously Miniconized Women

	Deceased n	Alive n
Malignancy of		
Breast	5	7
Uterus	2	2
Lung	2	1
Leukaemia/Mb. Hodgkin	2	1
Malignancy of		
Vulva	1	1
Vagina	1	
Ovary	1	2
Anus	1	4
Bowel	1	
Thyroid gland	1	
Infarct of the heart	2	1
Epilepsy	1	
Chronic hepatitis	1	1
Malignancy of		
Skin		7
Pancreas		1
Brain		1
Carcinoma in situ—vulvae		11
Carcinoma in situ—vaginae		5
Total	21 (0.88%)	45 (1.88%)

tion of the ovaries. Because of involved or uncertain margins, reconization with CO_2 laser was performed in 22 cases (Table 4) of which four were stage IA2 carcinoma and 12 IA1 malignancy. In five of the stage IA1 carcinomas, no additional therapy was given as no invasion of the capillary spaces was demonstrated and all had adequate margins. The remaining second treatments, such as "large" conizations, new LMC, or biopsy and cervical curettage, were done because of persisting CIN. Although 82 minimal cones had a positive margin, only 77 (3.2%) needed further treatment. The remaining five patients showed neither persistent nor recurrent CIN at the checkups. In spite of 2,726 cones with a free margin, ten specimens (0.37%) had persisting CIN.

The primary overall success rate with LMC by CO_2 laser was found to be 96.1%.

Hemorrhage following the LMC procedure occurred in 42 patients (1.45%). These bleedings were of minor degree and were managed either by touching the cervix with a vasoconstrictive mixture in most of the cases or, if necessary, by injecting the vasopressin analogue, lysine vasopressin (Postactone^R, Ferring, Malmö, Sweden) 10–20 ml solution (10 IU/ml Postactone^R, mixed

TABLE 4. The Significance of Involved Margins in the Minicones and the Primary Cure Rate in 2,903 Treated Women*

Margin	N	%	Second treatment n[a]	%
Positive	82	2.8	77	
Uncertain	95	3.3	25	
Free			10	
Total	177	6.1	112	3.9

*Primary cure rate for all CIN = 96.1%.
[a]Second minimal conization = 51; second (large) conization = 22; radical hysterectomy (Wertheim & Meigs) = 14; punch biopsy or/and cervical curettage = 25; Total = 112.

with 60 ml physiological saline). The majority of the 42 patients with postoperative hemorrhage (n = 35, 83.3%) showed coexistent cervicitis in their minicones at the histopathological examination.

Infections after LMC occurred in only two cases (0.07%).

During the 15-year follow-up, 47 middle aged or postmenopausal patients (2.0%) underwent hysterectomy because of recurrent CIN in 12 and unrelated gynecological causes in 35 women. During the follow-up period altogether 25,468 visits were made by 2,392 patients, giving a mean of 10.6 visits/15 years/woman, i.e., 1.5 years between visits for each woman. Posttreatment cervical phimosis occurred in 17 patients (0.71%) of whom 14 (82.4%) were elderly women and three were young women of fertile age. An additional two patients of childbearing age developed a tissue bridge between the 6 and 12 o'clock position on the cervix, which was easily divided as an office procedure at the first 6-month check-up.

The risk of CIN recurrence is illustrated in Table 5. The number of patients did not drop below 1,000 until year 11. The cumulative risks of developing a recurrence of all forms of CIN was 0.89%, 1.36%, and 3.02% at year 5, 10, and 15, respectively.

Unrelated deaths (n = 21, 0.88%) and intercurrent diseases are shown in Table 3. Both CIS vulvae and vaginae and also frank malignancies of the vulva, vagina, or anus were observed without simultaneous recurrence of CIN on the cervix.

During the follow-up period of 15 years, not a single patient with sudden-onset invasive carcinoma of the cervix was observed.

DISCUSSION

CIN, with its ability to develop into invasive carcinoma [8–13], often affects young women of childbearing age. To preserve both the anatomy and the physiology of the cervix, several different treatment modalities have been developed over the past 2–3 decades, of which laser ablation of the cervix has been the most commonly used for the past 10–15 years [1–3]. The minimal conization (LMC) procedure, however, was devised and published by Bekassy et al. as early as 1983 [4,5]. The principal difference ablative evaporation by laser and the LMC procedure is the fact that by LMC the entire tissue specimen removed containing all of the transformation zone, is available for histopathological investigation. Thus, the evidence of CIN or possible invasive carcinoma is not destroyed. The ultimate histological diagnosis before the laser ablation is based upon previous colposcopically guided biopsy, though this procedure cannot incontrovertibly guarantee a 100% certain diagnosis [5]. This difference between the two methods may explain why not even a single case of sudden onset invasive carcinoma was found during 15 years of follow-up following LMC, whereas several cases of invasive carcinoma have been reported following laser ablation [3]. The evidence of cancer undetected by previous colposcopically guided biopsy would be destroyed by laser ablation. Cancer cells, however, can survive ablation and subsequently develop a new carcinoma, hence causing the embarrassment known as the phenomenon of the mysterious "suddenly" appearing post-treatment invasive carcinoma.

A finding of invasive carcinoma in the minicones calls for adequate cancer therapy without delay. If eradication of CIN from minicones is completely successful the risk of developing an invasive carcinoma as verified in the present study over 15 years is entirely precluded. As regards the recurrence of CIN, no significant difference was observed in the distribution of patients by histologic grade CIN 1–3 (Table 5). The risk of recurrence of CIN of whatever grade after 15 years, albeit small at 3.02%, justifies long-term monitoring of cytological check-ups. However, the interval of 1.5–2 years between check-ups would appear to be sufficient, provided the histological investigation of minicones shows no involvement of the margins and the patient has normal colposcopy and cytology findings at the first check-up. In the paper by Lindberg et al. [14], a 2.71% abnormal cytology rate was found on rescreening initially negative women 4 years later. Once cured by minimal conization and having a normal cytology subsequently the patient is cytologically comparable with an initially negative woman.

TABLE 5. Risk of Recurrence of CIN After Minimal Conization by Laser

	All CIN			CIN 3/CIS			CIN 2			CIN 1		
Year	Woman-years	Recurrence	Risk %	Woman-years	Recurrence	Risk %	Woman-years	Recurrence	Risk %	Woman-years	Recurrence	Risk %
1	1,880	7	0.37	803	4	0.50	601	1	0.17	476	2	0.42
2	2,430	5	0.21	1,024	2	0.20	799	2	0.25	607	1	0.16
3	3,725	6	0.16	1,679	3	0.18	1,044	1	0.10	1,002	2	0.20
4	4,631	4	0.09	2,215	2	0.09	1,463	2	0.14	953		
5	3,419	2	0.06	1,650	1	0.06	996	1	0.10	773		
(cumulative risk)			(0.89)			(1.03)			(0.76)			(0.78)
6	2,206	2	0.09	988	1	0.10	634			584	1	0.17
7	1,757	1	0.06	838			482	1	0.20	437		
8	1,593	1	0.06	772	1	0.13	450			371		
9	1,324	1	0.08	644	1	0.16	377			303		
10	1,090	2	0.18	525			309	1	0.32	256	1	0.40
(cumulative risk)			(1.36)			(1.42)			(1.28)			(1.35)
11	613			299			175			139		
12	422	1	0.24	202	1	0.50	143			77		
13	248	1	0.40	115			79			54	1	1.86
14	98	1	1.02	43			38	1	2.63	17		
15	32			13			11			8		
(cumulative risk)			(3.02)			(1.92)			(3.91)			(3.21)
Total	25,468	34		11,810	16		7,601	10		6,057	8	

The cumulative risk of CIN recurrence in the present study after 5 years was 0.89%, i.e., much lower than Lindberg's figure. The interval of 2 years between check-ups also supports results published by Shy et al. [15], whose data suggest an increasing risk of cervical cancer if the cytologic screening interval exceeds 2 years.

The LMC procedure enables accurate histopathological investigation to be made of the entire transformation zone and facilitates early detection of invasive carcinoma. Diagnostic differences between pretreatment cytology and posttreatment histology are not mutually contradictory. On the contrary, abnormal cytology should serve as a warning bell for the clinician that, irrespective of the cytological CIN grade, the risk of invasive carcinoma of the cervix is present and should be excluded by resecting the entire transformation zone. This is to be recommended especially in patients in the age range 26–42 years (Table 2). The pretreatment colposcopy findings in the 35 cases of invasive carcinoma aroused suspicion of carcinoma in 30 (85.71%). Thus, although the histopathological diagnosis might have been achieved by colposcopically directed biopsy, the advantage of the LMC procedure, i.e., that the whole lesion would be primarily excised, giving the pathologist the opportunity to minutely investigate the depth of the stromal invasion and the invasion of the capillary spaces in the cones, facts which are partly the basis for the decision on the extent of the subsequent cancer treatment, cannot be overemphasized. In the present study, five patients with stage IA1 carcinoma in the minicones were cured primarily without the need for subsequent new treatment.

Healing after miniconization is rapid, causing neither immediate nor late complications. Postoperative hemorrhages, although few and not alarming, are the most common complication. Of all 42 patients with postoperative hemorrhage, 71.4% (n = 30) had evidence of associated cervicitis in their minicone. This inflammation was, however, of chronic type, without clinical signs of infection and without the need for further treatment. The presence of HPV in this study was not checked, but the incidence of both CIS and invasive carcinoma in the lower genital tract during the follow-up (Table 3) warrants further consideration. Post-treatment cervical phimosis is rare and occurs predominantly in elderly women.

Large loop electric excision of the transformation zone (LLETZ) frequently used during the last decade in treatment of CIN provides also tissue specimen for histopathology and like the LMC minimized the possibility of missing advanced le-

sions or microinvasive carcinoma [16,17]. Although the loop-cone is often removed in one piece, using LLETZ larger and irregular cervices require several sections resulting in more than one tissue specimen making the histopathological examination unneccessarily difficult [16]. Moreover, the margins of loop-cones can not be determined histologically in 5–30% of cases because of thermal damage [18].

The conclusion drawn from this study is that minimal conization by CO_2 laser is a safe, precise, and effective treatment modality for CIN and very early forms of stromal invasion. Invasive carcinoma can be detected immediately and subsequent appropriate cancer treatment is not delayed. Follow-up after minimal conization is reliable. After 15 years of follow-up in the present study, not a single case of sudden-onset carcinoma was observed, and the cumulative risk for developing new CIN was low, about 3%.

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